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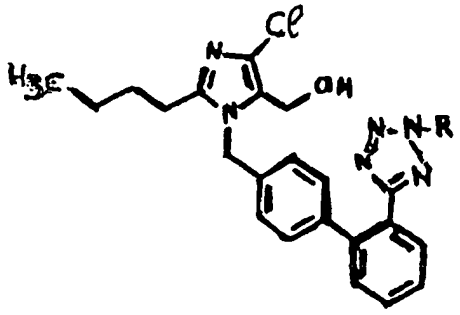
Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ,*

[Continued on next page]

(54) Title: PROCESS FOR THE CRYSTALLIZATION OF LOSARTAN POTASSIUM



(I)

(57) Abstract: There is disclosed a process to prepare crystalline Form (I) of Losartan Potassium which comprises: i) Reacting compound of formula (I). Where "R" represents hydrogen or triphenylmethyl (trityl) protecting group with potassium hydroxide in an alcohol, and ii) Concentration under reduced pressure to remove alcohol, and iii) Adding an anti-solvent to isolate Losartan Potassium.

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MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

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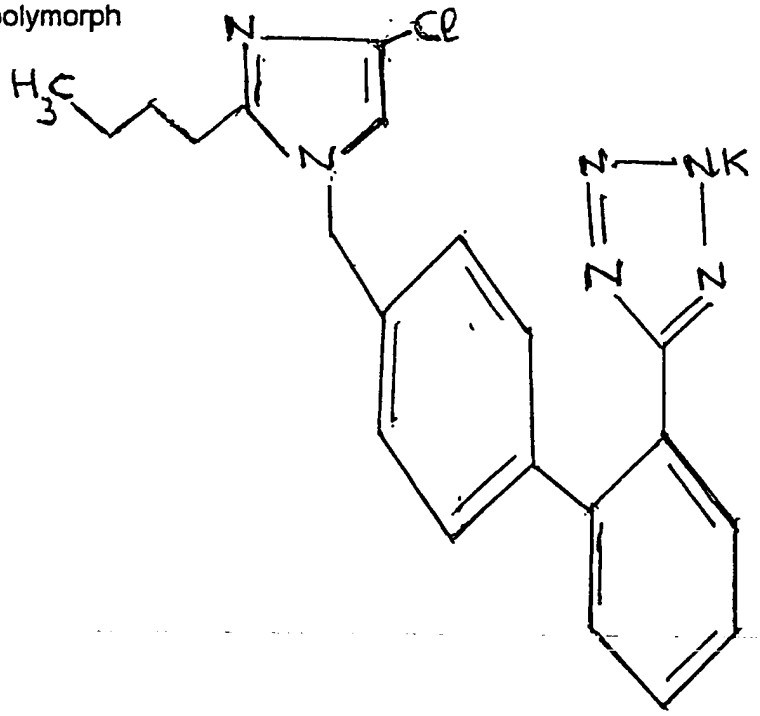
PROCESS FOR THE CRYSTALLIZATION OF LOSARTAN POTASSIUM

Field of the Invention:

This invention relates to a crystallization process to obtain losartan Potassium polymorph



Form I. Losartan is used in the treatment of hypertension.

Background f the Invention and Prior Art and Drawbacks:

This invention relates to crystallization process to prepare Losartan Potassium Form I. Losartan Potassium is also known as 2–n–butyl–4–chloro–5–hydroxymethyl–1- [[2'- (2H-tetrazole–5-yl) biphenyl–4-yl] methyl] imidazole potassium salt and is useful in the treatment of hypertension.

Losartan is known to inhibit the action of octapeptide hormone angiotensin II and is useful therefore in alleviating angiotensin induced hypertension. Further, it has been reported that losartan when administered with a diuretic such as furosemide or hydrochlorothiazide exhibits an enhanced anti-hypertensive effect. Administration of losartan with a non-steroidal anti-inflammatory drug can prevent renal failure.

Losartan is known to exhibit polymorphphism (Ref: US Patent 5,608,075). Two polymorphic forms of Losartan Potassium, Form I and Form II have been reported in US Patent 5,608,075 alongwith their methods of preparation. Characterization of these two polymorphic forms has been described through applications of X-ray powder diffraction pattern, DSC thermograms, FTIR spectra, Raman spectra and solid state ^{13}C NMR.

Polymorph Form I has been prepared in US Patent 5,608,075 by adding an aqueous solution of Losartan Potassium to a refluxing mixture of isopropanol/cyclohexene and removing water by distilling cyclohexene/isopropanol/water ternary azeotrope at 64° C. Losartan Potassium Form I crystallizes out at 69º C.

In WO 98/18787, a process to prepare polymorph Form I has been disclosed wherein solution of potassium salt in aqueous isopropanol is heated to lower the water content to about 2.6% by removing isopropanol/water mixture, immense seeding with Losartan Potassium slurry in cyclohexene is done until the seed remains undissolved and removing water to 0.02-0.11% by

distilling out the ternary azeotrope while simultaneously adding cyclohexene. The crystallized material is recovered by filtration.

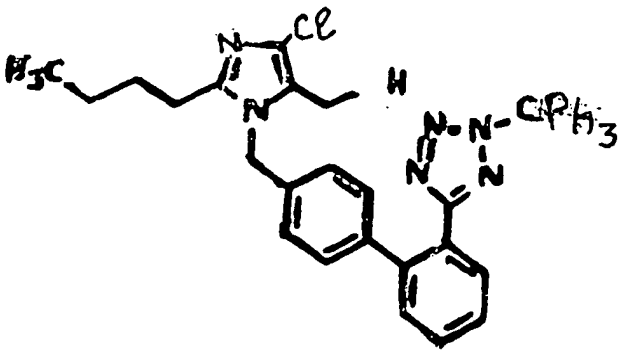
In both these disclosed processes, crystalline Losartan Potassium has been achieved from a mixture of isopropanol and cyclohexene and this crystalline material has been characterized as polymorph Form I. Crystallization process described in WO 98/18787 requires adequate precision to consistently obtain polymorph Form I and mixture of solvents, cyclohexene and isopropanol is difficult to separate. The inventors have surprisingly discovered that Losartan Potassium polymorph Form I can be prepared in one pot by reacting triphenylmethyl protected Losartan with Potassium hydroxide in methanol/acetone without isolating the free Losartan acid and requires no seeding.

Detailed Description of the Invention:

This invention relates to the process to manufacture Losartan Potassium Form I without use of isopropanol/cyclohexene solvent mixture. Typically Losartan free acid is suspended in a solvent and potassium hydroxide is added to obtain a clear solution, which is then concentrated under reduced pressure to remove most of the solvent. An anti-solvent is added to crystallize Losartan Potassium. The solvents to prepare Losartan Potassium include methanol, ethanol, butanol but preferably the salt formation is carried out in methanol. Anti-solvent is selected from common solvents such ethyl acetate, acetonitrile, toluene and acetone but the preferred anti-solvent is acetone.

Losartan free acid or triphenylmethyl protected Losartan may be prepared using the reactions and techniques described in US Patent 5,138,069 and WO 93/10106.

Alternatively, 2–n–butyl–4–chloro–5–hydroxymethyl–1- [[2'- [(2-triphenylmethyl) tetrazole–5-yl] biphenyl–4-yl] methyl] imidazole (herein referred as Trityl Losartan), a key intermediate



TRITYL LOSARTAN

in the manufacture of Losartan is refluxed with Potassium hydroxide in an alcohol, preferably methanol, to perform deprotection and generate in situ Losartan Potassium which is then isolated in desired polymorph Form I by distilling methanol and adding an anti-solvent such as acetonitrile, toluene, ethyl acetate and preferably acetone. Both the reaction and the crystallization may be effected in the same reaction vessel, and no expensive separation techniques, such as extraction or isolation of Losartan free acid are necessary. Such a process of obtaining Losartan Potassium polymorph Form I directly from Trityl losartan is not reported hitherto in literature and hence constitutes an object of the present invention. Additionally, the described preparation is done essentially under anhydrous condition and thus avoids elaborate azeotropic distillation for water removal. The desired polymorph Form I Losartan Potassium is obtained directly, that is, without having to isolate the free Losartan acid, which results in increased efficiency and contributes to the lower production cost.

Typically, trityl losartan is dissolved in 6-8 times by volume in methanol and equimolar quantity of potassium hydroxide is added. The resulting mixture is refluxed for a few hours till disappearance of trityl losartan is observed. Tritanol is recovered by filtration and methanol is distilled under reduced pressure. Acetone is added to the residue and distillation is continued to remove last traces of methanol. Losartan Potassium is obtained as a free flowing slurry in acetone that is

filtered and dried. The differential scanning calorimetric analysis and X-ray powder diffraction pattern confirm this to be polymorphic modification I.

The following examples further illustrate the preparation of Losartan Potassium polymorph form I and are not to be construed as any limitation thereof.

Example 1

100 gm. (0.152 mol.) 2–n–butyl–4–chloro–5–hydroxymethyl–1- [[2'- [(2-triphenylmethyl) tetrazole–5-yl] biphenyl–4-yl] methyl] imidazole (Trityl Losartan) was suspended in 650 ml. methanol. 10 gm. of 85% potassium hydroxide (0.152 mol.) was added and the mixture was refluxed under nitrogen atmosphere for nearly 6 hours. The reaction mass was cooled to 8-10° C and tritanol byproduct was removed by filtration and washed with 50 ml. chilled methanol. The filtrate was treated with 1 g. charcoal and filtered through celite. Methanol solution was then concentrated at 45-50° C to remove most of methanol. 200 ml. acetone was added and distillation continued under reduced pressure to reduce the volume to approximately 120 ml. The white crystalline slurry was cooled to room temperature, filtered and product washed with 50 ml. acetone and dried in vacuum oven to obtain Losartan Potassium. Yield: 60 g. (86.58% of theory). DSC analysis (Figure 1) and X-ray powdered diffraction pattern (Figure 2) comply with that reported for polymorph Form I.

Example 2

To a suspension of 5 gm. (11.82 m. mol.) 2–n–butyl–4–chloro–5–hydroxymethyl–1- [[2'- [(2H-tetrazole–5-yl] biphenyl–4-yl] methyl] imidazole (Losartan acid) in 25 ml. methanol, 0.75 g. (86%) (11.52 m. mol.) potassium hydroxide powder was added and mass stirred at ambient temperature to obtain an almost clear solution. This was filtered through celite and the clarified solution was concentrated to remove most of methanol at 45-50° C under reduced pressure. 25 ml. of acetone

was added and distillation continued to distil most of the methanol/acetone mixture. Residue was diluted with 25 ml. acetone and contents cooled to 20-25° C for 10 min and product filtered under nitrogen atmosphere and washed with 5 ml. acetone. Product was dried 55-60° C under reduced pressure to yield 4.88 g. (89.5% of theory) Losartan Potassium Form I (DSC, XRPD).

Example 3

To a suspension of 5 gm. (11.82 m. mol.) of Losartan acid in 25 ml. dry ethanol was added 0.75 g. (86%) (11.52 m. mol.) potassium hydroxide powder and mass stirred at ambient temperature for 25 minutes to obtain a clear solution. Ethanol was removed at 45-50° C under reduced pressure. 25 ml. of acetone was added and distillation continued to distil ethanol/acetone mixture under reduced pressure. Residue was stirred with 25 ml. acetone at 20-25° C and product filtered under nitrogen atmosphere and washed with 10 ml. acetone. Product was dried 55-60° C under reduced pressure to yield 4.85 g. (89% of theory) Losartan Potassium Form I (DSC).

Example 4

Losartan Potassium Form I was prepared from Losartan acid in methanol as described in Example 2 and ethyl acetate was used in place of acetone. Yield: 4.95 g. (91% of theory).

Example 5

Losartan Potassium Form I was prepared from Losartan acid following the procedure described in Example 2 and acetonitrile was added as anti-solvent to isolate the product. Yield: 4.8 g. (88% of theory).

Example 6

To a suspension of 5 g. Losartan in 25 ml. n-butanol, 0.75 g. of 86% powdered potassium hydroxide was added and the mixture was stirred at 20-25° C to get a clear solution. n-butanol ethanol was distilled under reduced pressure at temperature below 70° C. 25 ml. acetone was added and distilled under reduced pressure. Finally the contents were stirred in 25 ml. acetone at 20-25° C and filtered to obtain Losartan Potassium Form I. Yield: 4.8 g. (88% of theory).

Example 7

Losartan Potassium was prepared by reacting Losartan acid in n-butanol with potassium hydroxide as described in Example 6 and the product was isolated as polymorph Form I by addition of ethyl acetate as anti-solvent in place of acetone. Yield: 4.85 g. (89% of theory).

Example 8

Losartan Potassium was prepared in n-butanol as given in Example 6 and Form I of Losartan Potassium was isolated with toluene. Yield: 4.9 g. (90% of theory).

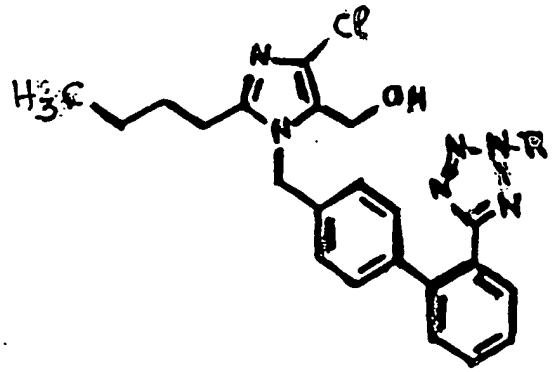
Example 9

Losartan Potassium was prepared in n-butanol as described in Example 6 and Form I was obtained by adding acetonitrile. Yield: 4.8 g. (88% of theory).

We claim:

1. A process to prepare crystalline Form I of Losartan Potassium which comprises

   i. Reacting compound of the formula.



   Where "R" represents hydrogen or triphenylmethyl (trityl) protecting group with potassium hydroxide in an alcohol, and

   ii. Concentration under reduced pressure to remove alcohol, and

   iii. Adding an anti-solvent to isolate Losartan Potassium.

2. A process according to claim 1 wherein exactly one mole equivalent of potassium hydroxide as to the staring compound is used.

3. A process according to claim 1 wherein alcohol is selected from the group consisting of methanol, ethanol, propanol, butanol and mixtures thereof.

4. A process according to claim 1 wherein the anti-solvent is selected from the group consisting of acetone, ethyl acetate, acetonitrile, toluene and mixtures thereof.

5. A process according to claim 1 wherein in situ de-protection is carried out to produce Losartan Potassium.

Dated this 12th day of November, 2001

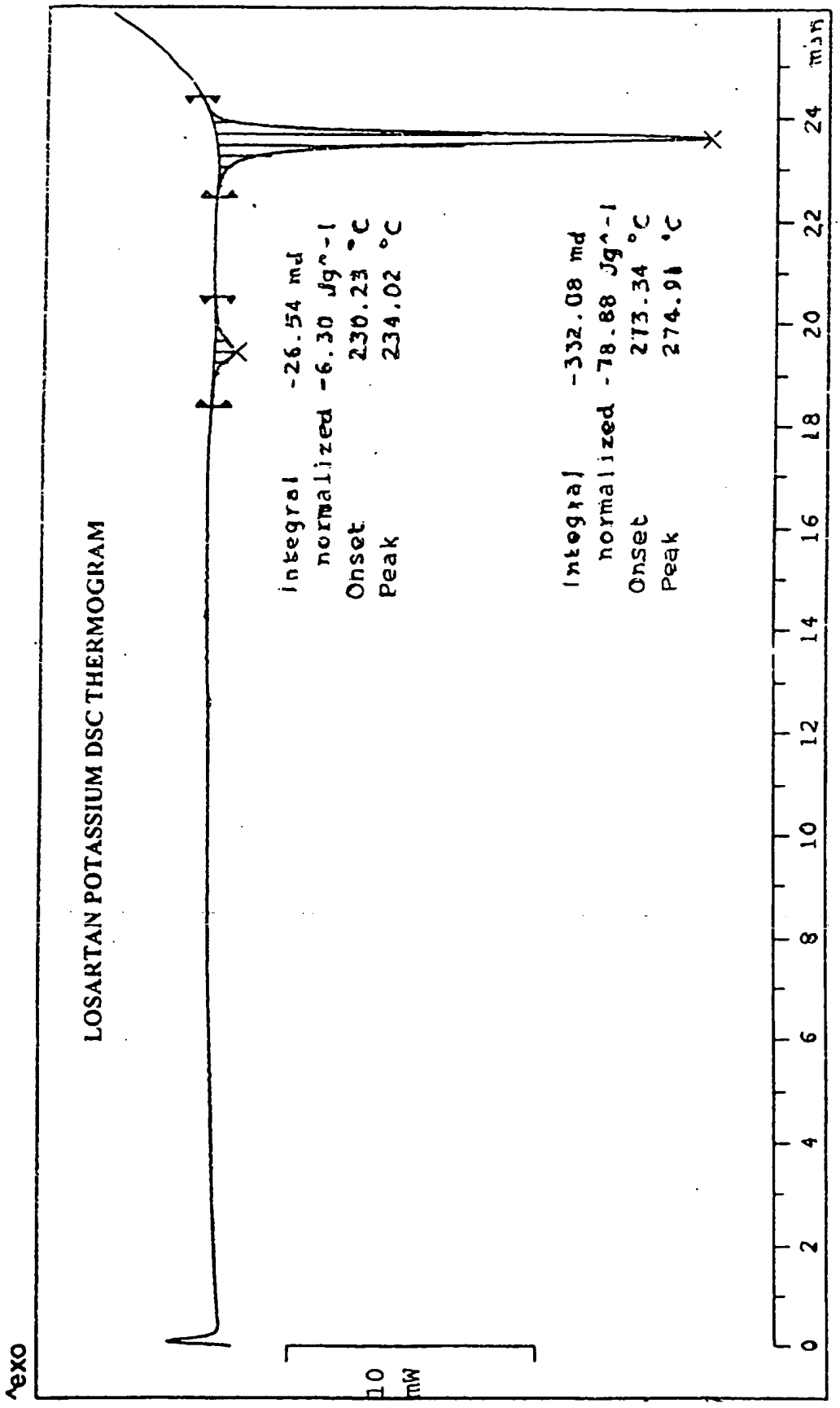
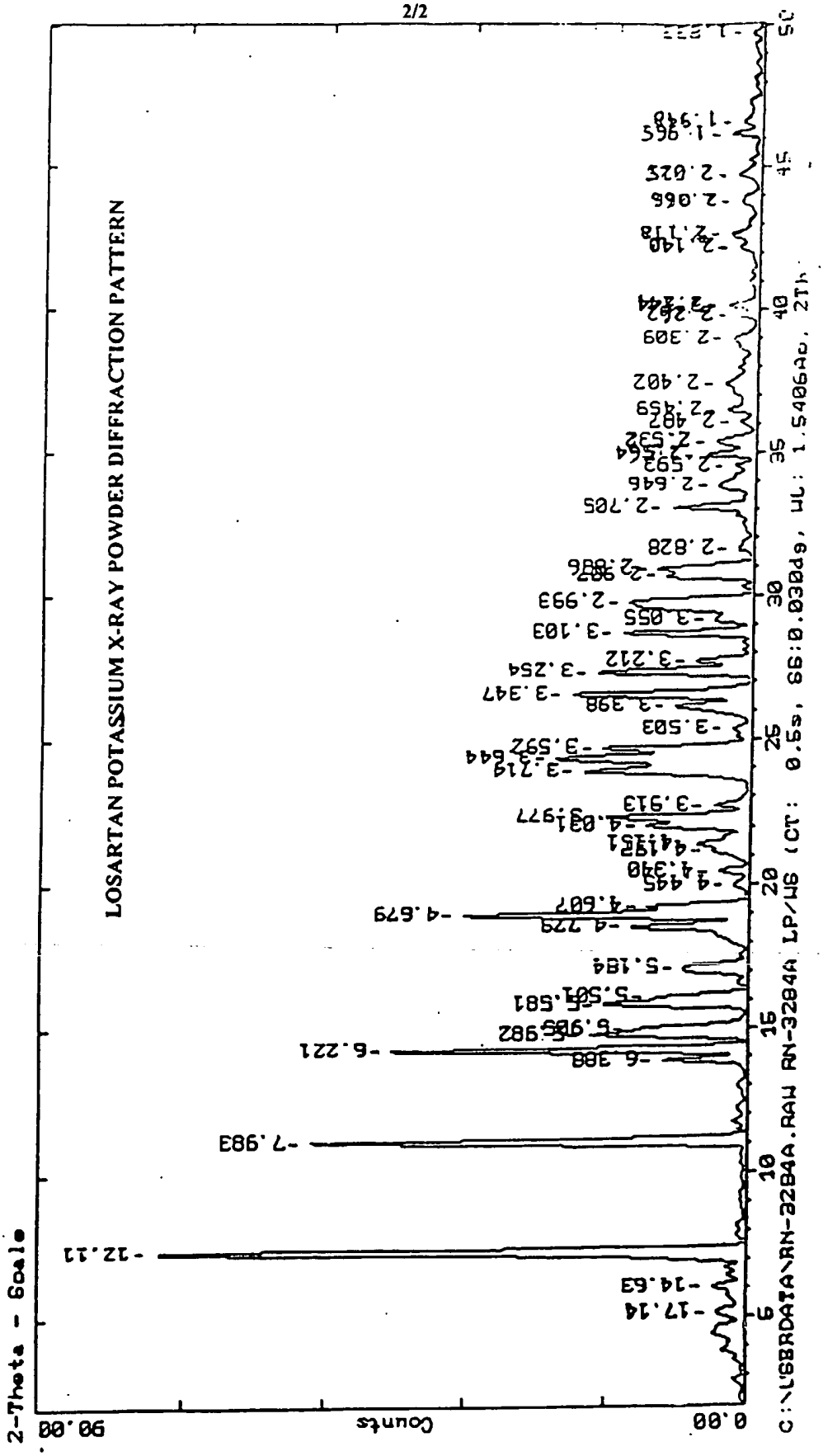

LOSARTAN POTASSIUM DSC THERMOGRAM
Integral -26.54 md
normalized -6.30 Jg^-1
Onset 230.23 °C
Peak 234.02 °C
Integral -332.08 md
normalized -78.88 Jg^-1
Onset 273.34 °C
Peak 274.91 °C
10 mW
exo
0 2 4 6 8 10 12 14 16 18 20 22 24 min

FIG. 1


LOSARTAN POTASSIUM X-RAY POWDER DIFFRACTION PATTERN
2-Theta - Scale
Counts
0.00
90.00
-12.11
-14.63
-17.14
-7.983
-6.221
-5.184
-4.679
-4.445
-3.913
-3.503
-3.398
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-2.646
-2.592
-2.564
-2.532
-2.459
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-1.948
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FIG. 2

INTERNATIONAL SEARCH REPORT

Inted ial Application No
PCT/IN 01/00205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 138 069 A (CARINI DAVID J ET AL) 11 August 1992 (1992-08-11) cited in the application	1-3
Y	examples 89,316	4,5
X	WO 93 10106 A (DU PONT ;MERCK & CO INC (US)) 27 May 1993 (1993-05-27) cited in the application	1-3
Y	examples 8,26	1-5
Y	WO 98 18787 A (KENNEDY MICHAEL T ;BREEN PATRICK (US); LARSON KAREN A (US); MAHADE) 7 May 1998 (1998-05-07) cited in the application page 4, line 24 -page 5, line 8; claim 1; examples	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2002	09/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Härtinger, S

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Inte ıal Application No
PCT/IN 01/00205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 81336 A (FARKAS JEN & ODBLAC ;FISCHER JANOS (HU); BALLO ILDIKO (HU); CZIBUL) 1 November 2001 (2001-11-01) claims; examples	1-5

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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